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DMPA-IM drives cervical Th17 HIV target cell accumulation in women in the ECHO trial

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Women randomized to **DMPA-IM** displayed an early increase in the abundance of highly susceptible **CD38+CCR5+α4β7+** Th17 HIV target cells in the female genital tract compared to women using the Cu-IUD or LNG-implant.

INTRODUCTION

To determine the association between HIV risk and DMPA-IM use, the Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial randomised women to three different contraceptives with HIV seroconversion as the primary endpoint. **Within ECHO, we evaluated the impact of contraceptive initiation on the abundance and phenotype of Th17 HIV target cells in the female genital tract.** Understanding the biological effects of widely used contraceptives remains important for development of refined contraceptive options with less controversial profiles.

STUDY DESIGN

ECHO Biological Mechanisms Sub-study

Emavundleni
Cape Town, South Africa

n=72

Cu-IUD n=23 | **DMPA-IM n=20** | **LNG implant n=15**

4 weeks

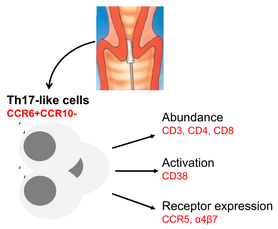
ECHO randomized women to copper-T intrauterine device (Cu-IUD), 150mg 3-monthly intramuscular DMPA-IM, and the 2-rod levonorgestrel (LNG) subdermal implant.

Participant characteristics at baseline

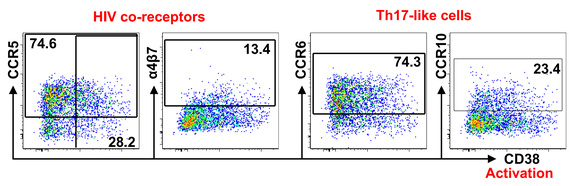
	Cu-IUD (n=23)	DMPA-IM (n=20)	LNG-implant (n=15)	p-value
Age*	22 (20-28)	24 (22-25)	22 (20-25)	0.80
BMI (kg/m^2)*	29 (26-38)	27 (23-32)	26 (22-32)	0.14
Days since last menstrual period	17 (11-27)	20.5 (10.3-29)	21 (12.3-30.5)	0.51
Genital infections [n(%)]				
Chlamydia trachomatis	4 (17.4%)	6 (30%)	4 (26.7%)	0.63
Neisseria gonorrhoeae	2 (8.7%)	3 (15%)	1 (6.7%)	0.75
Demographics [n (%)]				
Never married	23 (100%)	20 (100%)	14 (93.3)	0.26
Married	0 (0%)	0 (0%)	1 (6.7%)	
Primary school education	1 (4.3%)	0 (0%)	0 (0%)	0.71
Secondary education	22 (95.7%)	20 (100%)	14 (93.3%)	
Post-secondary education	0 (0%)	0 (0%)	1 (6.7%)	
Sexual risk behaviour in the last 3 months [n (%)]				
>1 partner	2 (8.7%)	4 (20%)	1 (6.7%)	0.46
1 partner	21 (91.3%)	16 (80%)	14 (93.3%)	
New partner	0 (0%)	4 (20%)	0 (0%)	**0.01**
Condomless sex	19 (82.6%)	13 (65%)	9 (60%)	0.31
Condom use (always)	4 (17.4%)	7 (35%)	6 (40%)	0.14
Condom use (often)	0 (0%)	0 (0%)	1 (6.7%)	
Condom use (sometimes)	13 (56.5%)	11 (55%)	8 (53.3%)	
Condom use (never)	6 (26.1%)	2 (10%)	0 (0%)	

*Median and IQR

CHARACTERISING T CELLS FROM THE GENITAL TRACT



Representative flow cytometry plots



	Marker	Channel
Dump channel	Live/Dead	Pacific Blue
	CD14	
	CD19	
Lineage	CD3	APC-H7
	CD4	PE-Cy5.5
	CD8	BV711
Activation	CD38	PE-Cy7
HIV receptor	CCR5	APC
	α4β7	PE
Th17-like cells	CCR6	BV605
	CCR10	Ax488

RESULTS AND DISCUSSION

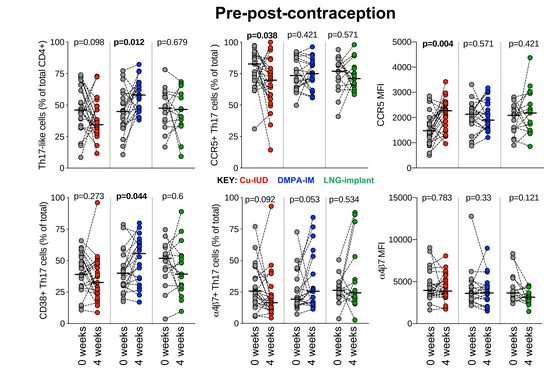


Figure 1: Overall frequencies of Th17 cells; Th17 cells expressing CD38, CCR5 or α4β7 pre-post contraceptive initiation (baseline and at one month) across randomization arms. The relative expression of CCR5 and α4β7 is also shown.

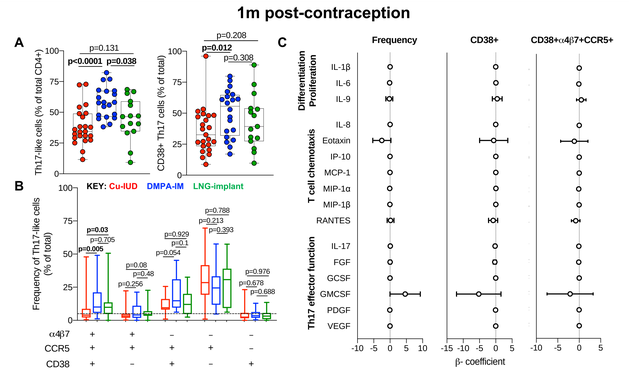


Figure 2: Th17 cells and cytokines after one month of contraception. Frequency of (**A**) Th17 cells and CD38+ Th17 cells and; (**B**) Th17 cells co-expressing markers. (**C**) Associations between Th17 cells and soluble cytokine concentrations in women using DMPA-IM (linear regression).

Pre-post changes

- Increased frequencies of the Th17 population, and CD38+ Th17 cells in women using DMPA-IM compared to baseline.
- Most cells in the FGT expressed CCR5 (>70%). CCR5+ Th17 was lower in women using Cu-IUD but the expression per cell (MFI) was higher.
- No other contraceptive-induced changes in the expression of CCR5 or α4β7.

At one month

- Women using DMPA-IM had higher frequencies of activated Th17 cells at one month compared to the Cu-IUD or LNG-implant.
- Increased frequencies of a highly susceptible Th17 population co-expressing CD38, CCR5 and α4β7 in women using DMPA-IM, compared to baseline (data not shown) and the Cu-IUD at one month.
- More activated Th17 cells did not correspond to increased concentrations of markers of T cell chemotaxis, proliferation, differentiation or Th17 effector cytokines and downstream growth factors. Thus, the increase in Th17 cells but not effector cytokines may indicate reduced Th17 function or a newly damaged epithelial barrier.

Discussion

- In the ECHO trial, women using DMPA-IM did not have an increased risk of HIV acquisition compared to women using the Cu-IUD and LNG.
- The observed increase in Th17 target cells might still be below the (undefined) minimum threshold required to increase HIV risk.

CONCLUSIONS

We observed significant increases in frequencies of susceptible populations of Th17 HIV target cells in women randomized to DMPA-IM 1 month after initiation, but not among women randomized to Cu-IUD or LNG-implant. In the ECHO Trial overall, DMPA-IM did not increase HIV risk suggesting that the changes to Th17 HIV target cells are of insufficient magnitude and/or duration to impact risk relative to the other contraceptives.

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